Remarks/Arguments

Claims 39-43 are pending in this application and were rejected on various grounds. Claim 39 has been amended for clarity. The rejections to the presently pending claims are respectfully traversed.

Priority

Applicants rely on the Skin Vascular permeability assay (Example 77) to establish patentable utility for the polypeptide PRO326. These results were first disclosed in international application PCT/US98/19437, filed 17 September, 1998 to which priority is claimed in this application. Support is found at Example 77, page 210, lines 22 onwards. Accordingly, the present application is entitled to the effective filing date of 17 September, 1998.

Double Patenting

Claims 39-43 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of co-pending Application No. 09/904,786.

Applicants hereby file a terminal disclaimer compliant with 37 C.F.R. 1.321(c) to overcome this rejection. Accordingly, Applicants request that this obviousness-type double-patenting rejection be withdrawn.

Claim Rejections – 35 U.S.C. §§101 and 112

Claims 39-43 remain rejected under 35 U.S.C. §§101 and 112, first paragraph, for alleged lack of a specific, substantial, credible asserted utility or a well established utility. As with the parallel nucleic acid and protein applications related to this molecule, the Examiner expressed that she was not clear and was somewhat confused with Applicants argument that the utility for PRO326 lies in its ability to cause inflammation. The Examiner alleged that the vascular skin permeability assay merely establishes that PRO326 is an 'irritant'. Further, the Examiner noted that the guinea pigs could be allergic to PRO326 due to presensitization to an epitope of PRO326. In a telephone

interview between Examiner Spector and Daphne Reddy, Ms. Reddy asserted that there was **no pre-sensitization** of the animal with human PRO326. Even so, the Examiner maintained that the allergic reaction could be due to prior exposure of the guinea pig to another "cross-reactive" antigen that shared an epitope with PRO326 and hence, the response could still be allergic. Finally, the Examiner points out that, based on the Rampart publication, the observation that PRO326 is an inflammatory molecule is merely a 'jumping off' point for further experimentation since the only inflammation that could be treated using anti-PRO326 antibodies is that actually caused by PRO326, which is a circular exercise with no meaning and does not constitute a substantial utility. Applicants respectfully traverse the above rejections.

Initially, Applicants would like to clarify that the utility for PRO326 and its variants is obviously not "to produce inflammation." As was asserted in the previous response, PRO326's utility lies in its use as a target for the development of anti-inflammatory agents (as is routinely done with other inflammatory molecules like prostaglandins, endothelins). As will be apparent from the discussions below, use of PRO326 antibodies as an anti-inflammatory agent would be in any acute neutrophil-mediated inflammation and not merely in PRO326 associated inflammation and is therefore, not a circular exercise.

Regarding the Examiner's point that the observed inflammation in guinea pigs is possibly "due to an allergic reaction," Applicants strongly disagree. Only for the sake of argument, without acquiescing to this rejection, Applicants address this issue by reviewing the criteria that differentiate between an allergen and a proinflammatory molecule, and by determining which of the criteria PRO326 meets. Criteria for a qualifying proinflammatory molecule is found, again, in Rampart *et al.* (See Rampart, column 1, Abstract)) that states that a proinflammatory molecule is characterized by:

"fast onset of neutrophil accumulation, short duration (half-life of 60-70 min) and parallel plasma leakage."

The characteristics of an allergic molecule can be found in any standard immunology text book. For example, see attached excerpt (especially pg 5, 12-9) from

Immunobiology by Janeway et al., (2001, Garland Publishing; Part V. The Immune System in Health and Disease, which says that an allergic molecule is characterized by:

> 1) an immediate IgE-mediated mast-cell activation based inflammatory response due to short-lived mediators like histamines and prostaglandins (needs prior allergen exposure), and, 2) a late-phase reaction (occurs after 8-10 hours), due to induced synthesis and release of mediators including leukotrienes, chemokines, and cytokines from the activated mast cells (emphasis added).

In the skin vascular permeability assay, Applicants have disclosed that PRO326 caused 1) blemishes in skin (which happens due to edema or plasma leakage), and, 2) cell inflammatory responses of neutrophilic, eosinophilic, monocytic or lymphocytic cells within 6 hr (fast onset). If, as suggested by the Examiner, PRO236 were an allergen, there should not have been an accumulation of neutrophils during the immediate short phase of the reaction, since immediate allergy-associated inflammation is mast cell-mediated and is not neutrophil-mediated. Instead, the involvement of neutrophils clearly demonstrates that PRO326 meets the criteria of a proinflammatory molecule and not that of an allergen. Thus, from the "skin vascular permeability" assay results, Applicants correctly concluded that PRO326 is a proinflammatory molecule.

Further, addressing the Examiner's concerns about "the conclusion of PRO326 as an inflammatory molecule, as a "jumping off point for further experimentation" (lack of enablement)", Applicants respectfully remind the Examiner that the level of skill, knowledge and the level of predictability in the art need to be considered before determining whether the amount of experimentation is undue. In *In re Wands*, the courts concluded that the amount of experimentation needed was not undue in view of the direction and guidance provided by the Appellants and the level of skill in the art (see below).

> "the court held that ....there was 'considerable direction and guidance' in the specification; there was 'a high level of skill in the art at the time the application was filed;' and all the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406; M.P.E.P. 2164.01(a)

Applicants submit that, unlike diseases like cancer, where the mechanism of action is considered unpredictable, and which have different causative mechanisms (and thus,

different molecular players) for each type of cancer, the key players and pathways associated with inflammation are few and are reasonably well understood in the art. From the data disclosed in the specification, specifically in the skin vascular permebablity assay, the skilled artisan would know that PRO326 is a proinflammatory molecule that attracts neutrophils besides other immune cells. Hence, they would know that anti-PRO326 would be useful against inflammations that involve immune cells like neutrophils (which include acute inflammations such as lung and renal inflammation, bacterial infections, etc.). While it is true that the skilled artisan would need to conduct experiments to determine the types of inflammation that PRO326 is primarily associated with, as in the *Wands* case, such experimentation is not undue for the skilled artisan. Applicants' guidance in the present disclosure together with the existing knowledge in the art at the time of filing, which was very high, sets a pre-determined path of experimentation for the artisan to follow. Moreover, the skilled artisan in the field of anti-inflammatory therapeutics at the time of filing was very sophisticated, as evidenced by the fact that they generally possessed either an M.D. or a Ph. D or both degrees in addition to vast experience. Instead, the skilled artisan would have found it routine to evaluate the types of inflammation for which anti-PRO326 antibodies would be useful. As discussed above, such antibodies would be useful in various neutrophil-mediated acute inflammations and therefore, this is a substantial utility.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claims 42 remains rejected under 35 U.S.C. §112, second paragraph, allegedly, as being indefinite for reciting the term "antibody fragment" by a definition other than the accepted definition. Applicants respectfully traverse this rejection.

In view of the cancellation of Claim 42, this rejection is moot and should be withdrawn.

Claim Rejections – 35 U.S.C. §102

1. Claims 39-43 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Wu et al., U.S.P.N. 6,046,030 (filing date 12/8/97).

Wu discloses a polypeptide (SEQ ID NO:5) having 50 % identity to residues 1-1083 of SEQ ID NO:294, not to the full-length sequence. Further, Wu does not teach an antibody that inhibits inflammation and specifically binds to SEQ ID NO: 294. Therefore, this reference is not anticipatory and Applicants respectfully request that this rejection be withdrawn.

2. Claims 39-44 were rejected under 35 U.S.C. §102(e) as being anticipated by Wang et al., U.S.P.N. 6,426,072 (filing date 8/21/00).

As discussed above, since Applicants are entitled to an effective filing date of 17 September, 1998, Wang is not prior art under 102(e) since its filing date is after the effective priority date.

Hence, Applicants respectfully request that this rejection be withdrawn.

Claim Rejections – 35 U.S.C. §103(a)

Claims 39-44 were rejected under 35 U.S.C. §103(a) as being unpatentable over Kawai et al. (6/1/01) or Nagase et al. (5/1/99) or Suzuki et al., (2/1/97) any of the three in view of Sibson et al. (WO 94/01548; filing date 1/20/94). The Examiner alleges that Sibson outlines generally that it is useful to place a desired cDNA sequence into an expression vector, host cell and to raise antibodies to the protein encoded by the cDNA. Thus, the Examiner alleges that it would be obvious to a person of skill in the art to make antibodies to any of the proteins disclosed by Kawai , Nagase or Suzuki according to the teachings of Sibson. Applicants respectfully traverse this rejection.

As discussed above, since Applicants are entitled to an effective filing date of 17 September, 1998, Nagase and Kawai fall as prior art.

Suzuki teaches a polypeptide that has 50.14% identity to the amino acid residues of SEQ ID NO: 294. Suzuki does not teach antibodies to their polypeptide nor that their polypeptide is associated with an immune or inflammatory response.

The claims in the present application are directed to antibodies which specifically bind to a PRO326 polypeptide of SEQ ID NO: 294 and which inhibit an inflammatory response. Suzuki, when taken alone or in combination, provides no suggestion or hint that the P70193 polypeptide would be associated with an inflammatory response, or would otherwise have biological properties similar to those of PRO326. As a result of the unexpected and unanticipated property of the polypeptide to which they bind, the antibodies of the present invention have the unobvious property of being able to inhibit an inflammatory response. Since this property is not disclosed or suggested in Suzuki, or its combination with Sibson, the present rejection is believed to be misplaced, and should be withdrawn.

Applicants also submit that the subject matter of the various claims in the present application were commonly owned at the time the invention was made.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-1618 P2C28**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 17, 2004

By: Daphne Reddy
Daphne Reddy (Reg. No. 53,507)

HELLER EHRMAN WHITE & McAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

477630v1